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EXAMINER	
HUMPHREY, DAVID HAROLD	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 06/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/633,484	RIDDER ET AL.	
	Examiner	Art Unit	
	David Humphrey	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-51 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-51 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-26, drawn to a method for diagnosing a medically relevant condition, classified in class 435, subclass 7.1, for example.

II. Claims 27-32, drawn to a test kit for diagnosing a medically relevant condition, classified in class 530, subclass 387.1, for example.

III. Claims 33-40, drawn to a method for diagnosing cervical dysplasia, classified in class 435, subclass 7.23, for example.

IV. Claims 41-46, drawn to a test kit for diagnosing cervical dysplasia, classified in class 436, subclass 501, for example.

V. Claim 47-51, drawn to a test kit comprising a reagent for detecting $p16^{INK4a}$ and a reagent for detecting gamma-Catenin, classified in class 435, subclass 344.1, for example.

2. The inventions are distinct, each from the other because of the following reasons:

The products of Inventions II, IV, and V are patentably distinct. Although there are no provisions under the section for "Relationship of Inventions" in M.P.E.P § 806.05 for inventive groups that are directed to different products, restriction is deemed proper because these products constitute patentably distinct inventions for the following reasons. Groups II, IV, and V, are directed to products that are distinct both physically and functionally, are not required one for the other, and are therefore patentably distinct. Invention II is drawn to a kit for diagnosing a medically relevant condition that contains

at least one marker for that condition. Invention IV is drawn to a kit for diagnosing cervical dysplasia. The markers used for diagnosing cervical dysplasia are not necessarily the markers used to diagnose another medical condition. Invention V is drawn to a kit for detecting p16INK4a. The reagents used in this kit are not necessary for Inventions II and IV. Therefore, Inventions II, IV, and V are patentably distinct.

The methods of Inventions I and III are patentably distinct. Although there are no provisions under the section for "Relationship of Inventions" in M.P.E.P. § 806.05 for inventive groups that are directed to different methods, restriction is deemed to be proper because these methods appear to constitute patentably distinct inventions. Invention I is drawn to a method of diagnosing a medical condition using markers for viral infections such as HPV L1 and HPV E1, for example, that are not required for Invention III. The method of Invention I also includes types of cancer such as head and neck, that are not required for Invention III. In addition, the method of Invention III utilizes the marker protein, claudin-1, which is not required for Invention I. Therefore, the methods of Invention I and III are patentably distinct.

Inventions II and I, IV and III, and V and III, are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the methods of Inventions I and III can be practiced using materially different products such as routine physical exams and histological examination of pap smears.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

REQUIREMENT FOR FURTHER RESTRICTION

3. If Applicants elect Invention I, further restriction is required. Claims 5, 8, 9, 10, 12, 13, 14, 15, 16, 19, 20, 23, 24, and 25, are drawn to method claims reciting different cancers, markers, and probes. Applicant is required to select a particular specific cancer, a particular specific disease marker, a particular specific normalization marker, AND a particular specific probe. **THIS IS NOT AN ELECTION OF SPECIES.**

I. Specific type of cancer recited in claim 5

a. Cancer of the head and neck;

b. Cancer of the respiratory tract;

c. cancer of the gastrointestinal tract;

d. cancer of the skin and its appendages;

e. cancer of the central and peripheral nervous system;

f. cancer of the urinary system;

g. cancer of the reproductive system;

h. anogenital cancer;

i. cancer of the endocrine system;

j. cancer of the soft tissues and bone; and

k. cancer of the lymphopoietic and hematopoietic sytem.

The cancers listed in a-k are patentably distinct. They have different etiological origins and require different treatment protocols.

II. One or more relevant markers recited in claim 8

aa. cell cycle regulatory proteins;

ab. Metalloproteinases;

ac. Transmembrane proteins;

ad. calcium binding proteins;

ae. growth factors;

af. marker molecules characteristic for viral infections;

ag. cell proliferation markers;

ah. markers associated with DNA replication;

ai. tumor marker proteins; and

aj-ar. nucleic acids coding for the respective proteins.

Applicant is required to select a particular specific combination of one or more specific markers (not to exceed 10) from ai-ar for examination. **THIS IS NOT AN ELECTION OF SPECIES.**

The different protein and DNA markers are patentably distinct because they are unique structures composed of different amino acid and nucleic acid sequences. The markers listed in aa-ar consist of different proteins and nucleic acids that are structurally unrelated, have diverse functional properties, and are therefore patentably distinct.

The search of any particular marker is not coextensive with the search of any other different marker and a reference against one marker is not necessarily a reference against any other marker. Applicant must elect EITHER one specific marker OR one specific combination of markers.

III. Tumor marker proteins recited in claim 9

ba. cyclin dependent kinase inhibitors;

bb. p53;

bc. PRb;

bd. P14ARF;

be. ARF;

bf. cyclin E;

bg. cyclin A;

bh. cyclin B;

bi. MN;

bj. her2/neu;

bk. mdm-2;

bl. bcl-2;

bm. EGF-receptor;

bn. MCM2;

bo. MCM3;

bp. MCM4;

bq. MCM5;

br. MCM6;

bs. MCM7;

bt. CDC2;

bu. CDC6;

bv. CDC7 protein kinase;

bw. CDC14 protein phosphatase;

bx. Dbf4;

by. PCNA;

bz. Ki67;

bba. KiS1;

bbb. Id1;

bbc. Osteopontine;

bbd. GRP;

bbe. Renal dipeptidase; and

bbf. TGFbetaII receptor.

The markers listed in ba-bbf consist of different proteins that are structurally unrelated, have diverse functional properties, and are therefore patentably distinct. A search of one protein is not coextensive with a search for any of the other proteins ba-bbf, and would therefore pose an undue search burden on the USPTO's resources.

IV. If Cyclin-depent kinases inhibitor is selected above in claim 9, Applicants must further choose one specific Cyclin-dependent kinase inhibitor recited in claim 10

ca. P16INK4a;

cb. P13.5;

cc. P14;

cd. P15;

ce. P19;

cf. P21; and

cd. P27.

The cyclin-dependent inhibitors listed in ca-cd consist of different proteins that are structurally distinct, are expressed in different tissues, and are therefore patentably distinct.

V. Viral protein or Viral DNA recited in claim 12

da. HPV L1 protein;

db. HPV L2 protein;

dc. HPV E1 protein;

dd. HPV E2 protein;

de. HPV E4 protein;

df. HPV E5 protein;

dh. HPV E6 protein;

di. HPV E7 protein;

dj. HPV L1 nucleic acid;

dk. HPV L2 nucleic acid;

dl. HPV E1 nucleic acid;

dm. HPV E2 nucleic acid;

dn. HPV E4 nucleic acid;

do. HPV E5 nucleic acid;

dp. HPV E6 nucleic acid; and

dq. HPV E7 nucleic acid.

The HPV proteins and nucleic acids of da-dq are separate and distinct. The HPV E5 protein is a small, hydrophobic protein embedded in cellular membranes which is capable of stimulating cell growth via enhancement of tyrosine-kinase growth factor receptor signaling pathways. However, HPV E7 oncoprotein has been shown to interact with p21Cip1 and overcomes p21Cip1 inhibition of the kinase activity of cyclin/cdk complexes.

While the HPV proteins are encoded by HPV nucleic acids, proteins and nucleic acids have substantially different physical, chemical, structural and functional properties. Moreover, they are made using different techniques and reagents and have materially different modes of operation in vivo. DNA, deoxyribonucleic acids are unbranched polymers composed of four subunits whereas polypeptides are a linear order of amino acid residues.

VI. One or more normalization markers recited in claims 13, 14, and 15

ea. Cell surface protein;

eb. Housekeeping genes;

ec. Receptor proteins;

ed. Glycoproteins and/or proteoglycans;

ef. Carbohydrate structures specific for glycoproteins and/or proteoglycans

eg. Cell cycle regulatory proteins;

eh. Metalloproteinases;

ei. Transmembrane proteins;

ej. Calcium binding proteins;

ek. Growth factors;

el. Cell differentiation markers;

em. Proteins associated with DNA replication;

en. Epithelial antigen;

eo. a cytokeratin;

ep. CD antigen;

eq. Glycoprotein;

er. Proteoglycan;

es. Carbohydrate structure on a glycoprotein or proteoglycan;

et. An enzyme involved in the biosynthesis of glycoproteins; and

eu. An enzyme involved in the biosynthesis of proteoglycans.

The normalization markers, ea-eu, include classes of patentably distinct proteins with different structures and functions. For example, the class calcium binding proteins includes: ALG2, BM40, calbindin D9k, calcineurin B, calcyclin, calmodulin, calpain and myosin regulatory light chain, to name just a few. Individual growth factor proteins tend to occur as members of larger families of structurally and evolutionarily related proteins. There are dozens and dozens of growth factor families such as TGF-beta (transforming

growth factor), BMP (bone morphogenic protein), neurotrophins (NGF, BDNF, and NT3), fibroblast growth factor (FGF), and so on.

Applicant is required to select a particular specific combination of one or more specific normalization markers (not to exceed 10) from ea-eu for examination. **THIS IS NOT AN ELECTION OF SPECIES.**

The different protein and DNA markers are patentably distinct because they are unique structures composed of different amino acid and nucleic acid sequences. The markers listed in ea-eu consist of different proteins and nucleic acids that are structurally unrelated, have diverse functional properties, and are therefore patentably distinct.

The search of any particular marker is not coextensive with the search of any other different marker and a reference against one marker is not necessarily a reference against any other marker. Applicant must elect EITHER one specific marker OR one specific combination of markers.

4. If Applicants elect Invention III, further restriction is required. Claims 34, 35, 39, and 40, are drawn to method claims reciting different markers, and probes. Applicant is required to select one relevant marker characteristic of cervical dysplasia, AND one normalization marker. **THIS IS NOT AN ELECTION OF SPECIES.**

VII. Relevant marker characteristic for the presence of cervical dysplasia recited in claim 34

fa. P16INK4a;

fb. HPV associated marker;

fc. P14 ARF;

fd. P19;

fe. P21;

ff. P27;

fg. PRb;

fh. P53;

fi. Cyclin E;

fj. Cyclin A;

fk. Cyclin B;

fl. MN;

fm. Her2/neu;

fn. Mdm-2;

fo. Bcl-2;

fp. EGF-receptor;

fq. MCM2;

fr. MCM3;

fs. MCM4;

ft. MCM5;

fu. MCM6;

fv. MCM7;

fw. CDC2;

fx. CDC6;

fy. CDC7 protein kinase;

fz. CDC14 protein phosphatase;

ffa. Dbf4;

ffb. PCNA;

ffc. Ki67;

ffd. KiS1;

ffe. Id1;

fff. Osteopontine;

ffg. Cladin-1;

ffh. GRP;

ffi. Renal dipeptidase; and

ffj. TGFbetaII receptor.

The markers listed in fa-ffj consist of different proteins that are structurally unrelated, have diverse functional properties, and are therefore patentably distinct. A search of one protein species is not coextensive with a search for any of the other proteins, and would therefore pose an undue search burden on the USPTO's resources.

VIII. Normalization marker characteristic for the presence of epithelial cells recited in claims 35, 39, and 40

ga. Gamma-Catenin;

gb. Ep-Cam;

gc. E-cadherin;

gd. Alpha-Catenin;

ge. Beta-Catenin;

gf. Desmoplakin;

gh. HKLK13;

gi. SCCA;

gj. UPA1;

gk. Involucrin;

gl. CK8;

gm. CK18;

gn. CK10;

go. CDK13;

gp. Vimentin;

gq. Concanavalin A receptor;

gr. Lectins;

gs. P120; and

gt. Involucrin.

The normalization markers ga-gt are patentably distinct proteins with different structures and functions. For example, Vimentin is an intermediate filament protein (58 kD) found in mesodermally derived cells (including muscle). Desmoplakin, on the other hand, is a key component of cellular adhesion junctions known as desmosomes (250/210 kD).

5. If Applicants elect Invention IV, further restriction is required. Claim 41 is drawn to a test kit reciting a detection reagent for different cervical dysplasia markers and a reagent for the detection of one normalization marker. Applicants are required to select one relevant marker characteristic of cervical dysplasia, AND one normalization marker. **THIS IS NOT AN ELECTION OF SPECIES.**

IX. Relevant marker characteristic for the presence of cervical dysplasia recited in claim 41

ha. P16 INK4a;

hb. P14ARF;

hc. Cyclin E;

hd. Cylclin A;

he. Cyclin B;

hf. MN;

hg. Her2/neu;

hi. Mdm-2;

hj. Bcl-2;

hk. EGF-receptor;

hl. Mcm-2;

hm. Mcm-5;

hn. Claudin-1;

ho. Markers indicative for human papilloma virus infection;

hp. PRb; and

hq. P53.

The markers listed in ha-hqf consist of different proteins that are structurally unrelated, have diverse functional properties, and are therefore patentably distinct. A search of one protein species is not coextensive with a search for any of the other marker proteins ha-hq, and would therefore pose an undue search burden on the USPTO's resources

X. Normalization marker characteristic for the presence of epithelial cells recited in claims 41

ia. CK8;

ib. Ep-Cam;

ic. CK13;

id. CK18;

ie. E-Cadherin;

if. Alpha-Catenin;

ig. Beta-catenin;

ih. Gamma-catenin; and

ii. Involucrin.

The normalization markers, ia-ii, are patentably distinct proteins with different structures and functions. For example, E-cadherin is a molecule involved in adhesion between epithelial cells that also seems to have a protective role in cancer, since its loss is associated with tumour progression and metastases formation in a series of different cancers. beta-catenin, but not E-cadherin, or alpha-catenin, becomes stabilized when proteasome-mediated proteolysis is inhibited and this leads to the accumulation of multi-ubiquitinated forms of beta-catenin. Involucrin is present in keratinocytes of epidermis and other stratified squamous epithelia and becomes cross-linked to membrane proteins by transglutaminase thus helping in the formation of an insoluble envelope beneath the plasma membrane.

6. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

7. Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

8. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Humphrey whose telephone number is (571) 272-5544. The examiner can normally be reached on Mon-Fri 8:30AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David Humphrey, Ph.D.

June 19, 2006

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER